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Schuurmans, Macé M ; Benden, Christian ; Inci, Ilhan

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DOI: <https://doi.org/10.4414/smw.2013.13773>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-92679>

Journal Article

Published Version

Originally published at:

Schuurmans, Macé M; Benden, Christian; Inci, Ilhan (2013). Practical approach to early postoperative management of lung transplant recipients. *Swiss Medical Weekly*, 143:w13773.

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Practical approach to early postoperative management of lung transplant recipients

Macé M. Schuurmans^a, Christian Benden^a, Ilhan Inci^b

^a Division of Pulmonology, University Hospital Zurich, Switzerland

^b Division of Thoracic Surgery, University Hospital Zurich, Switzerland

Summary

Meticulous attention to detail during the early postoperative period after lung transplantation is crucial for the overall success of the procedure. It starts in the intensive care unit with the initiation of immunosuppression, implementation of anti-infective strategies and stabilisation of respiratory function. The subsequent days and weeks on the regular ward focus on titration of immunosuppressive drugs, vigilant fluid management, early mobilisation and initiation of physiotherapy. In parallel, the lung transplant recipients are actively taught about self-monitoring and self-management strategies to allow for a smooth transition to outpatient follow-up care. This article intends to communicate the practical aspects and principles of the patient management used at the authors' centre on a daily basis by a multi-disciplinary transplant team, having at its core both a transplant pulmonologist and a thoracic surgeon. It focuses on the first month after lung transplantation, but

does not cover surgical techniques, rare complications or long-term management issues of lung transplant recipients. The target audience of this practical guide are advanced trainees of pulmonology, thoracic surgery, intensive care, anaesthesiology and other clinicians involved in the early postoperative care of lung transplant recipients either in the intensive care unit or on the peripheral ward.

Key words: lung transplantation; postoperative; management; practical; infection; complication; medication

Introduction

Lung transplantation is an established therapeutic option for nonmalignant end-stage lung disease. Survival of lung transplant recipients (LTRs) is inferior to recipients of most other solid organ transplants owing to the great number of complications in the first postoperative year. Some complications may be preventable or easy to correct if treated appropriately; however, in many situations management strategies are less clear because firm evidence from systematic evaluation or randomised controlled trials is not available. Many therapeutic strategies are based on expert opinion only or modified from experience with other solid organ transplant recipients, and some have stood the test of time after being adapted for LTRs. In the few available articles and book chapters covering the early postoperative management, the amount and level of detail of practical guidance varies considerably [1–3]. Many publications focus on an analytical approach, investigating, for example, aetiology, pathophysiology and therapeutic measures in the early postoperative phase. However, these articles generally do not mention the practical aspects of implementation with direct relevance to the attending physician. As a matter of fact, there are no guidelines for the management of the early postoperative period after lung transplantation [1, 4–7]. This article presents a practical approach on how to manage LTRs in the immediate postoperative phase, based on the authors' centre experience, providing evidence to support this practice wherever available [8]. It is our aim to share our experience with colleagues new to the field and stimulate discussion and open up potential research areas

List of abbreviations

CsA	cyclosporine A
BID	twice a day
C0	cyclosporine trough level
C2	cyclosporine peak level
CRP	C-reactive protein
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CF	cystic fibrosis
CXR	chest x-ray
ECMO	extracorporeal membrane oxygenation
EBV	Epstein-Barr virus
FEV ₁	forced expiratory volume in one second
FVC	forced vital capacity
HSV	herpes simplex virus
ICU	intensive care unit
INHAL	by inhalation
IV	intravenous
IVIG	intravenous immunoglobulin
LTR(s)	lung transplant recipient(s)
MMF	mycophenolate mofetil
PCR	polymerase chain reaction
PTLD	post-transplant lymphoproliferative disease
TID	three times a day
TDM	therapeutic drug monitoring
VZV	varicella-zoster virus

of interest on how to best treat our patients. Rare complications and mostly surgical issues including indications for surgical reintervention are not dealt with here [9]. We are aware that there are various successful ways to manage these patients in the early postoperative period, and this is only one possible strategy that is influenced by available resources and local expertise generated over twenty years.

The first postoperative days

After successful transplantation, recipients are routinely transferred to the intensive care unit (ICU) immediately from the operating theatre. Generally, patients are still intubated and some might even require postoperative extracorporeal membrane oxygenation (ECMO) support. Weaning from both ventilator and ECMO is primarily in the hands of the intensive care physicians, but usually in consultation with the thoracic surgeon and transplant physician, as are basically all other aspects of care [10, 11]. Independently of the level of experience of the intensivists in charge, twice daily ICU ward rounds by the transplant team are of vital importance in order to assist with monitoring the patient's clinical status and to obtain a cross-functional update on the patient's progress, including vital parameters, early immunosuppression, monitoring of wounds/drains, nursing information and physical therapy. Ideally, at least one daily ward round should be attended by a senior thoracic surgeon, a transplant physician and the ICU consultant in charge, as a team. In some settings the infectious disease specialist is part of daily transplant team rounds since infections are among the most frequent complications in this period. We have a dedicated transplant infectious diseases specialist who is consulted on a demand basis.

Initial immunosuppression and antimicrobial therapy

A key issue of the successful management of LTRs is the establishment of adequate immunosuppression in order to prevent acute allograft rejection, while at the same time avoiding over-immunosuppression with deleterious consequences. In general, a standard triple immunosuppressive regimen is used, with initial dosing having been discussed at the time of listing the patient for lung transplantation [12]. Calcineurin inhibitors (CNIs), especially cyclosporine A (CsA) and tacrolimus (Tac), are cornerstones of the immunosuppressive strategy. There are good arguments for both agents with a majority of lung transplant centres now using Tac as first line CNI [13]. They have a different effect on cardiovascular risk factors, with Tac having a better profile for arterial tension and lipid metabolism, and CsA for glucose metabolism. At present, data on whether these differences in risk profile alter patient or graft survival or long-term cardiovascular morbidity/mortality are scarce [14]. In a recent multicentre randomised study comparing CsA with Tac, the incidence of chronic rejection at 3-year follow-up was reduced in the Tac-containing regimen without significant effects on mortality [15]. Tac-treated patients may more often experience alopecia, whereas CsA is associated with hirsutism and gingival hyperplasia [16].

CsA is our drug of choice because of our many years of experience with the intricacies of this compound, and we reserve Tac for rare situations as a second-line CNI. In addition, perioperative antibiotic therapy is based on the individual patient's previously isolated airway pathogens and the established antibiogram. The antibiotic regimen is adapted by the transplant physician while the patient is on the waiting list if new pathogens are isolated or sensitivity patterns change. The revised antibiotic therapy regimen is updated in the clinical information system, and is thus available to the transplant surgeons at time of transplantation. Special issues are discussed in the weekly interdisciplinary meeting, such as the need for intraoperative sampling of lung tissue or lymphnodes for special examination (microbiology, mycobacterial diagnostics, pathology) or specific anti-infective preventive strategies (taurodin use intraoperatively, etc.). Immunosuppressive medication is started immediately before surgery with the first dose of oral CsA approximately 2 hours before anaesthesia (2 mg/kg). Steroids and mycophenolate (MMF) are initiated postoperatively according to our centre's protocol as previously published, for example MMF 1.5 g for a 70 kg adult patient [17]. Both are continued postoperatively at 12-hour intervals. At our institution, induction therapy is employed (basiliximab 20 mg on both day 0 and day 4). Immunosuppression includes methylprednisone 500 mg IV given at the time of reperfusion for each lung (two doses for bilateral transplantation, total 1 g) followed by 125 mg methylprednisone intravenously on days 1 and 2 after surgery. While intubated, LTRs receive CsA and MMF via a nasogastric tube whereby all preventive measures for gastroesophageal reflux are maintained. In general, from day 3 onwards, prednisone 0.5 mg/kg is given orally or via postpyloric tube. If LTRs are not extubated by day 2 or 3, a duodenal tube is inserted by the gastroenterologist. From day 2 onwards, the CsA dose is adjusted on the basis of therapeutic drug monitoring (TDM), with initial target levels of 250–300 mcg/L for C0 (CsA trough level) and 1100–1200 mcg/L for C2 (CsA peak level). In the case of renal dysfunction, lower target levels are used: 180–200 mcg/L for C0 and 750–800 mcg/L for C2. If adequate levels are not reached within 3–4 days we change to intravenous (IV) administration of CsA, especially in the case of transient increased variability of intestinal drug absorption (due to altered intestinal transit times i.e. diarrhoea or obstipation). The same is true for suspected insufficient absorption of MMF (either by means of TDM or because of lack of lymphopaenia) and steroids, which then are given intravenously until the clinical condition allows for stepwise reintroduction of the triple immunosuppression by the oral or enteral route [18]. Owing to the low bioavailability of CsA, the IV dose is nominally only approximately one-third of the oral dose. If immunosuppressants are given enterally, we use the syrup solution diluted in 2–3 ml noncarbonated mineral water for CsA and MMF, prednisone tablets are ground and suspended in mineral water before ingestion. For obstructed enteral tubes we use one ampoule of ascorbic acid or 3 ml Cola soft drink to free the system.

Infection prevention strategies

LTRs are prone to infection because of the specific circumstances of the allograft and the profound immunosuppression [19]. Bacterial pneumonia is frequent, especially in the first month [19, 20]. Therefore, antimicrobial therapy is administered to all LTRs, starting intraoperatively with a broad-spectrum antibiotic such as piperacillin-tazobactam or meropenem. We do not routinely cover for Gram-positive organisms unless sampling suggests such pathogens. In cases with known *Pseudomonas aeruginosa* (PSA) infection, a dual antibiotic strategy is chosen on the basis of previous antibiograms, generally including one of the above drugs in combination with either ciprofloxacin, an aminoglycoside (amikacin or tobramycin) or colistin IV. If multiresistant PSA is present, we may use a triple antibiotic strategy, in which inhaled colistin or tobramycin, or taurolidine are used in addition. We use taurolidine exclusively in cystic fibrosis (CF) patients after lung transplantation with multiresistant or panresistant bacteria (PSA or *Burkholderia cepacia* complex). A 1% solution is replaced with a 2% solution if well tolerated, and nasal and oral inhalation routes are alternated. This use is off label and not supported by large clinical trials, yet in our experience it has proven valuable [21]. Drug sensitivity testing is a crucial component of the antimicrobial strategy to better target the above mentioned organisms [22]. As part of our anti-infective regimen, LTRs with CF generally undergo sinus surgery (bilateral frontosphenoidectomy) within a few weeks after lung transplantation, aiming to reduce the potential for pulmonary contamination as recently described [23].

Pneumocystis jiruvei pneumonia (PJP) prophylaxis is started immediately after transplantation, with trimethoprim-cotrimoxazol one full strength tablet 3 times per week. Antifungal therapy in the perioperative phase is also based upon on the pretransplant assessment of the recipient. If *Aspergillus* species or a combination of multiple fungal organisms has been documented, we opt for early use of caspofungin also to prevent anastomotic problems [9, 17]. In documented pretransplant aspergillus infection of the recipient or presence of *Aspergillus* in the donor samples, we start caspofungin immediately awaiting further microbiological results (IV 50 mg daily without loading dose).

Regular antifungal therapy with itraconazole (200 mg BID) and inhalation of amphotericin B (10 mg BID) is usually started on day 5–7 postoperatively. In situations of transient apparent overlap of the antifungal spectrum (itraconazole plus caspofungin) we do not interrupt itraconazole transiently for reasons of interaction stability, thus maintaining a stable immunosuppression [18, 24, 25]. We recommend an inhalation device producing a medium particle size in order to reach the large and medium-size bronchi (e.g. Pari Boy SX with blue LC Sprint Aerolizer). If Amphotericin B inhalations trigger bronchial obstruction, a bronchodilator (salbutamol) is used before inhaling the antifungal solution.

Additional antibiotics or changes of the antimicrobial therapy are targeted on the organisms detected in the explanted lungs and the samples taken from the donor bronchus at transplantation [19]. We have a low threshold for seeking

clostridial infection in stool samples since *Clostridium difficile* colitis is common in the first 3 months [26]. If clostridial infection is suspected, we empirically start with oral metronidazole (500 mg TID) pending stool results and discontinue this therapy if results are negative. Exceptionally, we use oral vancomycin for this purpose (to avoid interaction with CsA). Pronounced leucocytosis associated with clostridial infection may indicate a higher severity and require additional measures such as IV immunoglobulin (IVIG) [3].

Prophylactic viral medication is given on the basis of the level of risk for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infection, which depends on the recipient/donor status [27]. Patients at high-risk for CMV (recipient negative/donor positive (-/+)) for CMV are treated immediately postoperatively with IV ganciclovir (250 mg BID) in combination with IVIG for the first 2–3 weeks, followed by oral valganciclovir (450 mg BID). Intermediate risk (+/+ and +/-) is covered initially with IV ganciclovir followed by oral treatment. In low risk scenarios (-/-), we use valaciclovir, which is effective against herpes viruses other than CMV. IVIG is given in very high-risk constellations and in case of CMV disease/reactivation. Should cytopenia (particularly leucopenia) occur, or progressive renal failure develops, the valganciclovir dosage is reduced. Patients at high risk for EBV infection (-/+)) we treat with valaciclovir (500 mg BID) if no valganciclovir is given (due to a high or intermediate risk for CMV). There is limited evidence to suggest that this strategy prevents EBV-related disease [28].

Post-transplant lymphoproliferative disease (PTLD) is a feared complication of profound immunosuppression in LTRs. Most cases of PTLD are related to the EBV. The major risk factor for PTLD is primary infection among individuals who are EBV-seronegative prior to transplantation and whose source of infection is usually an EBV-seropositive organ (EBV mismatch). The vast majority of adult transplant candidates are EBV-seropositive, whereas in children EBV-mismatch appears to be more prevalent [28]. Passive immunoprophylaxis is accomplished by providing of anti-EBV antibodies in the form of IVIG. Chemoprophylaxis with available antivirals is not proven beyond doubt to be efficacious. These antivirals do not clearly affect EBV in its latent state nor influence proliferation of EBV-transformed B cells. The strategy of choice appears to be viral load monitoring and pre-emptive strategies of prevention including reduction of immunosuppression as initial step when viral load increases [28].

Primary prophylaxis of other herpesviruses such as herpes simplex virus (HSV) and varicella-zoster virus (VZV) is achieved by the CMV prophylaxis, in our case valganciclovir [29].

As a rule, we use a limited number of compounds we know well and for which we have acquired considerable experience with the interaction patterns and their expected dose adjustments, as recently published [15]. In addition, we aim to administer all drugs required in the morning and evening timeslots (12 hours apart), thus simplifying the process for patients and aiming to increase compliance. In the early postoperative period, the number of drugs is so high, so that three to four timeslots for drug intake are required. An

exhaustive thesaurus of compounds we commonly use has been published recently [18]. On the other hand, we have compiled a list of drugs of which we discourage the use in LTRs in an attempt to prevent complications (table 1).

Aspects to check on daily ward rounds

During ward rounds, the transplant team takes into account all aspects related to the patients' polymedication, which allows for continuous adjustments of medication and optimisation of accompanying therapeutic measures: before assessing the vital signs and clinical parameters at the bedside, we discuss laboratory and imaging results. The ICU physician and nurse update the transplant team on the most recent developments, and the further management plan is then discussed. Aspects routinely discussed during this visit are summarised in table 2. One issue that needs special attention is intestinal motility, which frequently is reduced by many factors (drugs, immobilisation, etc.). Since obstipation or coprostasis generally remains asymptomatic or oligosymptomatic initially, and complications are potentially severe, we emphasise the need for daily bowel movements from postoperative day 2 onwards, and therefore provide adequate administration of laxatives. Osmotically active laxatives (such as macrogolum 3350) and radiocontrast agents (natrii amidotrizoas/meglumini amidotrizoas orally 20–40 ml three times daily) and, especially in CF patients, oral high dose N-acetyl-cysteine (up to 5 g per dose, mixed with orange juice to attenuate the bad smell/taste). With this strategy we aim to prevent some of the early severe gastrointestinal complications [30, 31].

Appropriate analgesia in the early postoperative phase is crucial, and frequently opioids are indicated. In the ICU, remifentanyl or fentanyl are used in the first hours or days, respectively. In awake patients morphine is titrated to the individual needs by a patient controlled analgesia system. The IV analgesics are discontinued when the recipient is transferred to the regular ward in order to reduce opioid adverse events. A combination of metamizole and paracetamol at fixed intervals (3–4 times per day) is used as baseline analgesia [32]. If pain control is insufficient, as assessed with a visual analogue scale, oral opioids are given in addition: oxycodone/naloxone (10/5 mg) in a fixed combination every twelve hours and oxycodone drops as required. This regimen is constantly re-evaluated, with the aim of a timely discontinuation whenever clinically pos-

sible. In protracted strong pain, we tend to add venlafaxine or trimipramine to raise the pain threshold.

For both psychiatric and/or psychological complications, an experienced psychiatrist and psychologist are available for intervention in the early postoperative phase, since anxiety disorders, adaptation disorders, transient confusion and depressive reactions require evaluation, support and sometimes medication. For depression and frequent sleep disorders we use sertraline, citalopram, trimipramine, mirtazepin and dipiperone [18]. Both the psychiatrist and the psychologist take part in our interdisciplinary ward meeting, where all LTRs are discussed in the presence of the nurse in charge, the transplant team, and physiotherapist, nutritionist and occupational therapist.

Antireflux measures are considered a high priority in the early postoperative phase, with reverse Trendelenburg positioning of the patient at all times in order to prevent gastroesophageal reflux and aspiration [33]. We do not specifically investigate for reflux, since we assume that it is present in all LTRs, who therefore receive prokinetic and antacid medication as well as lifestyle advice on how to prevent reflux. It is not always feasible to maintain this tilt position consistently on ICU when measurement of central venous pressure in a horizontal position is required. We aim to reduce such measurements to a minimum if the patient's condition allows for it. In general, proton-pump inhibitors are prescribed twice daily from immediately after transplantation, as well as the prokinetic domperidone TID before meals. Some centres perform reflux studies and fundoplication operations [34].

Fluid and weight management

LTRs frequently show a tendency to be fluid overloaded in the first postoperative days, manifested by substantially increased weight in most cases (typically 10%–15% increase in body weight) and oedematous tissue typically in, but not limited to, the lower limbs. Among other factors, early postoperative hydration with IV fluid to prevent prerenal kidney failure while on CNI therapy contributes [35]. We aim for a careful negative fluid balance in this phase, with cautious use of diuretics (not surpassing a weight reduction of >1 kg/day). We provide protein-rich nutrition to most LTRs since almost all our LTRs have documented hypoalbuminaemia postoperatively. Lack of lymph drainage in the transplanted lung additionally requires careful fluid man-

Table 1: Inappropriate medication for early postoperative treatment of lung transplant recipients.

Medication (example)	Comment/reason
Calcium antagonists (amlodipine)	Oedema frequently observed in LTRs
Nitrates (transcutaneous preparations)	Headache problematic, no long-term antihypertensive
Nonsteroidal anti-inflammatory drugs (ibuprofen, diclofenac, mefenamic acid, naproxen, etc.)	Nephrotoxicity increased in combination with cyclosporine/tacrolimus
Probiotics (<i>Saccharomyces boulardii</i>)	Potential infectious complications under severe immunosuppression
Fluconazole, voriconazole	Strong interactions with immunosuppressants, photosensitisation and potential role in promoting skin cancer
Antidiarrhoeal medication (any)	Only exceptionally used because of risk of obstipation
Short-term use of macrolides	Because of interaction with CNIs. Long-term use (clarithromycin) with TDM of CNI is possible. Azithromycin has the lowest interaction potential.

LTRs = lung transplant recipients; CNI = calcineurin inhibitor; TDM = therapeutic drug monitoring.

Inappropriate medications are avoided in our setting. Rarely do we use these medications in situations where monitoring of interactions and adverse events can be guaranteed. Some centres use some of these drugs with appropriate caution.

agement as the tendency to pulmonary oedema is increased in LTRs. Physical measures such as bandaging or compression stockings are used. LTRs are informed that resolution of leg oedema usually takes weeks and is enhanced by increased mobility.

Low-dose heparin is given to all LTRs until discharge unless oral anticoagulation is required for thromboembolic disease, arrhythmia or preoperatively diagnosed substantial pulmonary hypertension. Both diuretics and CNIs increase urinary magnesium excretion, thus magnesium needs to be replaced routinely in order to maintain high normal serum levels. The intracellular magnesium level may be low despite normal serum levels. Magnesium is an essential cofactor in numerous cellular functions that influence, for example, muscle function and gastrointestinal motility. We routinely measure electrolytes, kidney function, liver values, signs of infection/inflammation (C reactive protein (CRP), selectively procalcitonin) and CsA levels (C0 and C2), initially daily, in the stabilisation phase 3–4 times weekly [36]. In addition, CMV and EBV viral load, using polymerase chain reaction (PCR), as well as serum level of itraconazole and MMF are measured weekly in the first month after the transplant [37]. Immunglobulin levels including subclasses are determined once postoperatively before administration of IVIG.

Chest imaging

Chest x-rays (CXR) are useful to detect early and delayed complications and to guide their resolution (table 23). In unclear situations, we additionally perform chest computed tomography (CT) (without contrast agent) to visualise unclear findings [38, 39]. A potentially fatal early postoperative complications with suggestive features on CXR is primary graft dysfunction, which may present as diffuse pulmonary oedema and/or by mimicking an acute respiratory distress syndrome [3, 40, 41]. At our centre, we initially perform chest radiography every day (first week). On average, two CXRs are taken per week in the 2nd and 3rd week postoperatively, more frequently if clinically indicated. The decision for thoracic imaging also depends on the chest tube management. Removal of the drains is performed if drainage <200 ml/24 h. Lung expansion and potential new fluid collections have to be monitored. Chest tube removal is a stepwise process depending on daily

chest tube drainage. Apical drains are removed first. The correct drainage and fixation of remaining tubes has to be checked by the transplant team daily on ward rounds.

Primary graft dysfunction has been defined as a triad of worsening gas exchange, decreased lung compliance, and alveolar and interstitial infiltrates typically most extensive in perihilar regions, within the first 72 hours [42]. Differential diagnoses are acute rejection, infection, venous anastomosis complications, and cardiogenic pulmonary oedema. When primary graft dysfunction is diagnosed, we use protective lung ventilation, cautious fluid management and in severe cases inhaled nitric oxide (10–40 ppm) to reduce hypoxia and elevated pulmonary arterial pressure. Potential drawbacks of inhaled nitric oxide are methaemoglobinemia and cytotoxicity from free radical production [43]. If these strategies are insufficient, we use veno-venous extracorporeal membrane oxygenation (ECMO) [42].

Acute cellular rejection with lymphocyte-predominant inflammatory infiltrates around vessels and/or airways, occurs rarely in the first month postoperatively. If infection has been excluded by means of bronchoalveolar lavage, and lung tissue samples obtained by transbronchial biopsy show significant acute cellular rejection, we give high-dose corticosteroid pulse treatment for 3 days (IV methylprednisolone approximately 10 mg/kg/day). In the case of suspected antibody-mediated rejection, we would additionally provide low-dose IVIG (approximately 100 mg/kg as a weekly dose, usually 10 g). Strategies to treat primary graft dysfunction and acute rejection are variable and lack firm evidence. For acute rejection, additional strategies such as monoclonal antibodies, plasmapheresis, photopheresis, total lymphoid radiation and change of CNI medication have been used to influence the short- and long-term outcomes.

Should signs of infection or inflammation (i.e. CRP elevation) occur without an apparent focus, it is advisable to proactively search for the site of infection or inflammation by performing broad sampling using a defined routine strategy as “septic screen” [18, 44]. We have a low threshold for replacing indwelling catheters (central or peripheral drip lines) in particular if lines are *in situ* for longer than 7 days [20, 45].

Table 2: Radiological presentation of postoperative complications after lung transplantation over time.

Time and type of complication	Frequent radiologic features
Immediate (<24 hours)	
Abnormality due to malposition of postoperative lines and tubes	Pneumothorax, haemothorax, haemomediastinum, lung collapse, barotrauma
Diaphragmatic paralysis (due to phrenic nerve damage)	Elevated hemidiaphragm
Size mismatch between donor lung and recipient thoracic cage	Atelectasis or hyperinflation
Hyperacute rejection	Massive infiltration of lung parenchyma
Early (24 hours to 1 week)	
Reperfusion injury	Perihilar haze, peribronchial thickening
Pleural complications	Hemothorax, pneumothorax, empyema
Acute rejection	Ground-glass opacities with intra- and interlobular septal thickening
Bacterial pneumonia	Lobar or diffuse consolidation, cavitation, nodules
Intermediate (8 days to 2 months)	
Bronchial dehiscence	Perianastomotic air leak or flap and bronchial wall irregularity or narrowing
Fungal pneumonia (<i>Candida</i> , <i>Aspergillus</i>)	Irregular nodules, ground-glass and airspace opacities, consolidation
Cytomegalovirus pneumonia	Nodules, ground-glass or reticular opacities and consolidation
Modified from [39]	

Stabilisation and patient education phase on the ward

Once extubated, and depending on the course of the immediate postoperative phase, LTRs are transferred as early as day 2 to the regular transplant ward for further care. The emphasis of management in the following days is on fine-tuning immunosuppression, introducing additional prophylactic medication, removal of all chest tubes, and increasing physiotherapy and mobilisation. Education of patients regarding medication, lifestyle issues, self-monitoring and self-management issues is described in our centre as “teaching” (table 4).

When optimising the immunosuppression, the metabolic interaction of other compounds has to be taken into account. The most important medications prone to interact with immunosuppressants in this early postoperative phase are itraconazole, esomeprazole and sometimes metronidazole. These drugs generally increase CNI levels; thus CNI doses need to be reduced and adjusted accordingly on the basis of C0 and C2 levels. The CNI drug dose reduction is generally by one-quarter to one-third after approximately 4 days.

Under the necessary profound immunosuppressive therapy, wound healing is delayed so that removal of suture material is in general postponed until week 3 postoperatively to allow for sufficient healing. In LTRs previously requiring

ECMO support, local wound healing complications at the cannulation sites (inguinal, anterior chest wall or jugular region) occur frequently: infection or lymphatic fistula manifest as skin erythema or protracted secretion of lymph, respectively. Sometimes conservative measures are insufficient so that surgical revisions have to be undertaken.

Despite seemingly optimal fluid management, LTRs increase their bodyweight postoperatively, sometimes by more than 10%, owing to fluid management, immobility, inflammatory conditions and vascular leakiness resulting in fluid accumulation in the third space, typically in the lower extremities. Therefore, in the stabilisation phase, cautious fluid management with consideration of the above-mentioned contributing factors in combination with careful use of diuretics is mandatory to reduce the body weight, with the aim of gradual weight loss by 1 kg /day. Certain drugs appear to increase leakiness in our LTRs, which we therefore avoid particularly in this initial phase (calcium antagonists, i.e. amlodipine, see table 1). Because of immobility and increased risk of thromboembolic events, LTRs receive prophylactic IV heparin (generally 10000 IU/24h) from day 0 to the day of discharge unless specific reasons exist to establish therapeutic anticoagulation (such as recent thromboembolic events or severe pulmonary hypertension preoperatively).

Fluid management may be complicated by heart failure, which is sometimes due to atrial fibrillation. Atrial fib-

Table 3: Checklist and comments for intensive-care-unit and ward rounds visiting lung transplant patients.

Item to be checked	Comments / suggested action or medication
Clinical assessment: Weight, temperature, blood pressure, pulse, stool frequency, nausea or vomiting? Oedema? Positioning of patient?	Weight gain is common in first postoperative days, fluid overload predisposes to pulmonary oedema (diuretics). Stool retention (generous laxative treatment). LTRs are prone to reflux and aspiration, therefore positioning in tilt position (reverse Trendelenburg)
Respiratory system: Cough, sputum production, respiratory rate, ventilation parameters, blood gases	Sputum samples or tracheal aspirates taken for analysis?
Neurologic deficits? Adequate pain control? Level of consciousness?	Polyneuropathy? Special care and occupational therapy required? Vitamin substitution? Neurological work-up required? Is adverse event due to medication?
Chest tubes. Drainage rate, colour, leakage. Chest x-ray	Removal if drainage amount <200 ml/24h and concomitant weight loss observed. Signs of chest tube obstruction? Signs of haemothorax, atelectasis or infection?
Laboratory values: CRP, creatinine, electrolytes, glucose, FBC, C0/C2, microbiology results from recipient and from donor	Signs of cytopenia? Lymphocytes reduced? Adjustments needed for cytopenia-causing drugs? Any new pathogens recognised (recipient or donor)? Are they sufficiently covered by current antibiotic/antifungal regimen?
Medication: CsA dose adjustments based on therapeutic drug monitoring: Trough level (C0) and peak level (C2) Other drugs	Immunosuppression: Drug levels? Are all recommended drugs being given? Calcium and vitamin D supplements? Any inappropriate medication being used? Correct timing? Interacting drugs are all taken at two time-points separated by 12 hours (8 a.m./8 p.m.)
CMV and EBV PCR results? Other infections?	Level of risk for CMV-infection/disease? Signs of overimmunosuppression or insufficient prophylaxis? Additional samples required? (blood, urine, stool cultures, indwelling catheter)
Immunoglobulin levels?	Hypogammaglobulinaemia? Recurrent infections? IVIG needed?
Nutritional status?	Pre-albumin, albumin, protein, weight
Vascular access sites after cannulation in upper chest or inguinal locations	Signs of wound complications? Signs of lymph fistula? Involve vascular surgeon.
Prevention of venous thromboembolic disease	Adequate medication and physical measures (compression stockings or bandaging)?
Tracheostomy cannula	Complications? Still required? Decanulation? Healing after removal?
Sutures/staples	Removal after 10–21 days, usually by first removing every second staple.
Psychological/psychiatric condition	How is patient dealing with new situation? Depression? Coping strategies? Psychiatric consultation required? Psychological support needed? Sleep medication?
Level of self-monitoring and medication?	Results? Cystic fibrosis: sinus washes being done?
LTRs = lung transplant recipients; CRP = C-reactive protein; FBC = full blood count; CyA = cyclosporine A; C0 = trough level of cyclosporine; C2 = peak level of cyclosporine; CMV = cytomegalovirus; EBV = Epstein-Barr virus; PCR = polymerase chain-reaction; IVIG = intravenous immunoglobulin.	

rillation is common in the early postoperative phase and can have a number of possible aetiologies [46]. During the ICU stay atrial fibrillation is usually rapidly detected and treated. Delayed onset atrial fibrillation may occur when the LTR is in the regular ward. Therefore, any unexplained heart failure, hypotension or tachycardia merits an electrocardiogram. Besides the therapeutic anticoagulation and correction of electrolyte levels, rhythm control is attempted first with metoprolol: if that is insufficient we give amiodarone [2]. Only when amiodarone is insufficient do we perform electroconversion. Unlike others we do not use digoxin because of its interaction profile.

Physiotherapy and home spirometry

Physiotherapy starts early during the ICU stay and focuses on the positioning of the patient, ventilation of all lung lobes and mobilisation of secretions by managing cough. The slight reverse Trendelenburg position is maintained at all times as part of the antireflux measures. Upright positioning of the patient and mobilisation out of the bed is performed as soon as possible. Exercises to increase cardiorespiratory function (walking or cycle ergometry) follow once some or all chest drains have been removed. Often patients have to be reminded that both the muscular and cardiovascular systems need a more gradual increase in exercise intensity as these systems have been underused as a result of the limitations of the respiratory system. The main aims of physiotherapy and the modalities used are summarised in table 5. Besides a cycle ergometer, the Thera[®] Band, a scarf-like latex band, is sometimes used to enhance muscular function in this phase. It is useful when patients are unable get up alone from bed because of general weakness or multiple drains and infusion lines. LTRs receive instructions for exercises they can perform alone between daily physiotherapy sessions. Deep-breathing techniques and the use of the home spirometry equipment is taught unless recent tracheostomy decannulation or closure was performed. We then delay spirometry measurements by 7–10 days.

Home spirometry serves to measure and document forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) twice daily (best of three attempts), an important part of the self-monitoring programme [47].

Whether once or twice daily spirometry is critical can be debated. For this period, we believe it is beneficial since repetition and supervision allows improvements in technique. The increase in lung function measurements in the first weeks after the transplant serves often as strong motivator and indicator of success for LTRs. After discharge, the measurements are used to track pulmonary function and detect potential early deterioration before the patient subjectively notices any dyspnoea during activities of daily life. Recipients are instructed to contact the transplant team if the FEV₁ declines by 10% or more at two subsequent timepoints. This will prompt investigation for signs of infection and allograft rejection [18]. The first surveillance bronchoscopy, with bronchial wash at the anastomotic regions, bronchoalveolar lavage, and transbronchial biopsies, is performed before discharge after transplantation. This procedure is repeated monthly in the first half year and serves to identify anastomotic problems, infections and early signs of allograft dysfunction. Results help adjust immunosuppressive and anti-infective treatment. We do not use protected brush specimen sampling. Timing of surveillance bronchoscopies varies and many centres do not perform these in favour of clinically mandated bronchoscopies. Both strategies have their merits [48].

Some patients have had a prolonged ICU stay before or after transplantation. Critical illness polyneuropathy or myopathy may occur and frequently require long-term and intensified physiotherapy as well as occupational therapy, with the aim to improve both motor and sensory function and to enable activities of daily living. In these patients, we sometimes use incentive spirometry or the Acapella[®] airways clearance device (Smiths Medical Inc, Carlsbad, California, USA) to enhance lung expansion and mobilisation of secretions, respectively. Referral to inpatient rehabilitation programmes is very rare and limited to these patients with critical illness polyneuropathy or sequelae of a cerebrovascular event. All other LTRs are discharged home and receive outpatient physiotherapy or rehabilitation.

Teaching self-monitoring and self-treatment

To limit rehospitalisation and long-distance travel for patients, it has proved useful to instruct LTRs how to admin-

Table 4: Some teaching topics for lung transplant patients.

Medication issues	All medications are explained, including adverse events Importance of 12 hourly intake and simultaneous intake of drugs that interact with CsA (i.e. itraconazole, clarithromycin, metronidazole). Self-medication: laxative treatments, importance of sufficient fluid intake and increased intake when high ambient temperatures, analgesia options, avoiding NSAIs and opioids. Vomiting within 1 hour of drug intake (immunosuppressants), take them again and call transplant centre for advice.
Nutritional issues and topics specific to cystic fibrosis	Allowed and not allowed foods, rationale (list). Examples: grapefruit, raw meat and fish not allowed. Low carbohydrate diet is explained for LTRs at risk of obesity Cystic fibrosis: pancreatic enzyme substitution; fat-soluble vitamin substitution, laxative management, procedures for cleaning nasal sinuses (Clyso pump, technique, rationale, hygiene), diabetes instruction.
Sun protection and persistent skin lesions	Avoid outdoor activity between 11 a.m. and 3 p.m. Sunscreen as daily cream. Hat with brim and long-arm/long-leg cloths. Self-examination and importance of once yearly check-up in specialised dermatology clinic. Any wound or skin lesion that does not resolve within 3 weeks needs to be shown to specialist.
Self-monitoring	Home spirometry technique and documentation. Instructed to call transplant team if FEV1 decreases by 10% or more at two subsequent daily measurements. Weight and temperature documentation (elderly, cardiac failure, obese, prone to infection). Blood pressure documentation.

CsA = cyclosporine A; NSAID = nonsteroidal anti-inflammatory; LTRs = lung transplant recipients; FEV1 = forced expiratory volume in 1 second.

ister IV antibiotics at home if indicated. After studying our written instructions (specifically adapted to the self-therapy situation), LTRs observe the nurses handling the infusions and also perform the task under supervision by staff. Before giving permission to administer home IV treatment, the transplant coordinators check the patients' abilities to perform the procedures safely and apply strict hygiene rules.

This approach allows us to have an IV access put in by the local healthcare provider with subsequent administration of the antibiotics by the patients as previously instructed.

In general, instructing patients about general lifestyle issues, self-monitoring and self-treatment is referred to as "teaching" and is an important element in our postoperative care. This information is partly given in writing, as a brochure (No. 1) before definitive evaluation for lung transplant, a further brochure (No. 2) during work-up for transplantation associated with two or three teaching sessions, and a final brochure (No. 3) after transplantation with at least three teaching sessions given to two or three patients (under exceptional circumstances individually) by the transplant coordinator. Each session lasts 1–1.5 hours. Although patients are instructed preoperatively about many aspects of lung transplantation, these topics are covered once again in depth after the procedure. Frequently, a relative (parent, son or daughter) or partner is included in these teaching sessions in order to provide optimal care and support for the first months after discharge. This support person is especially important in the extremes of ages (very young and old LTRs). Sometimes additional teaching sessions are required when evaluation after three meetings shows insufficient patient knowledge. For a number of topics covered in greater detail during the teaching sessions, LTRs receive preprinted paper with topics and space provided to be filled in by the LTR during teaching.

Teaching topics cover a great number of themes of which only the most important are mentioned here (table 5); many aspects are centre-specific [49]. In our opinion, the following aspects are also important: preparation of medication dosing boxes for 7 days in advance, conservative antireflux measures and maintaining a good intestinal function as key to successful long-term allograft survival. We also emphasise in what situations and how to contact the lung transplant team at all times.

Acknowledgement: We would like to thank Drs. Dieter Scholtze, Jean-Luc-Kurzen (Pulmonology Fellows) and Renato

Lenherr (ICU consultant) for their comments regarding this manuscript and Thomas Locher and Sandra Brueren (Physiotherapists) for sharing their treatment principles. Our management principles have been set up and developed over two decades by multiple members of our transplant team.

Funding / potential competing interests: No financial support and no other potential conflict of interest relevant to this article was reported.

Correspondence: Macé M. Schuurmans, MD FCCP, Division of Pulmonology, C-HOER 23, Raemistrasse 100, CH-8091 Zurich, Switzerland, [mschuurmans\[at\]me.com](mailto:mschuurmans[at]me.com)

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Table 5: Physiotherapy objectives and techniques used in the early postoperative phase after lung transplantation.

Indication, objective and method	Timeframe and details
Often tachypnoea and pursed-lips breathing persist postoperatively. Chest physiotherapy, deep breathing exercises.	Atelectasis prophylaxis, conscious breathing pattern to overcome old breathing pattern and techniques.
Diaphragm training:	Sniffing exercises (inspiratory) and tonification exercises (breathing in different body positions) Coughing technique
Pain control and muscle relaxation, improving posture and balance	Exercises to relax muscle groups (in the case of pain, muscle tension or dysfunction), including chest, back and spine regions.
Oedema management	Lower extremities frequently oedematous, external compression provided by bandaging daily (acute phase) or compression stockings (stabilisation phase)
Muscle strength and function, endurance training. Main focus lower extremities. For upper extremities weight limit 3 kg initially.	Focus is improved muscle function: Walking, stair climbing, stepper, cycle ergometer. Sometimes bed cycling equipment. Thera-Band exercise band training (individualised): Stretching exercises.

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